

Figure 1. Methylphenidate (MPH) enhances functional magnetic resonance imaging (fMRI) cingulate responses and reduces commission errors on a salient (cue reactivity) cognitive task in individuals with cocaine addiction. On the left are axial maps depicting caudal–dorsal anterior cingulate (cdACC, BA 24, 32) and rostroventromedial anterior cingulate (extending to the medial orbitofrontal cortex, rvACC/mOFC, BA 10, 32) cortical regions that showed enhanced responses to MPH as compared with placebo (PL) in cocaine-addicted individuals. On the right is a graph showing the correlation between % blood oxygenation level-dependent (BOLD) signal change from a fixation baseline as a function of drug words in the rvACC/mOFC (x = -9, y = 42, z = -6, BA 10, 32) and the respective change in accuracy on the fMRI task (both are delta scores: MPH minus placebo). Subjects are 13 individuals with cocaine use disorders and 14 healthy controls.

task performance in CUD consistent with the cognitive benefits of MPH in other psychopathologies. In CUD, we speculate that these effects reflect MPH-induced increases in dopamine neurotransmission in these dopaminedeficient individuals. Specifically, we postulate (based on preclinical electrophysiological studies) that MPH increased SNR by enhancing dopamine (perhaps also noradrenergic) neurotransmission, thereby enhancing the activation of regions involved in the task (ACC). Although clinical trials with MPH have not been effective in decreasing cocaine use in CUD, these results suggest that MPH may have therapeutic benefits in facilitating behavioral modification (eg, impulse control) when combined with specific cognitive interventions.

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#### DISCLOSURE

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- Goldstein RZ, Alia-Klein N, Tomasi D, Carrillo JH, Maloney T, Woicik PA *et al* (2009). Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. *Proc Natl Acad Sci USA* **106**: 9453–9458.
- Goldstein RZ, Tomasi D, Rajaram S, Cottone LA, Zhang L, Maloney T *et al* (2007). Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience* **144**: 1153–1159.
- Goldstein RZ, Volkow ND (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* **159**: 1642–1652.
- Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW (2000). Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci* **20**: RC65.
- Volkow ND, Fowler JS, Wang GJ, Swanson JM (2004). Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry* 9: 557–569.
- Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Wong C et al (2008). Methylphenidate

decreased the amount of glucose needed by the brain to perform a cognitive task. *PLoS ONE* **3**: e2017.

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## Failures in Learning-Dependent Predictive Perception as the Key Cognitive Vulnerability to Psychosis in Schizophrenia

Cognitive deficits present in almost all patients with schizophrenia, and account for considerable functional disability, but as typically measured in schizophrenia are unrelated to hallucinations and delusions. The absence of this relationship may be caused in part by the lack of an organizing principle of psychosisrelated cognitive impairment. Most studies of cognition in schizophrenia involve standard neuropsychological tests that were devised for measuring brain injury in patients with no previous relevant illness. Human perception, thought and action-the basic elements of maintaining reality-are based upon a hierarchical process that conjoins memory and external stimuli, which we refer to as learningdependent predictive perception. We

propose that impairments in this elemental process lead to psychosis in patients with schizophrenia.

The hierarchical model posits that the nature of the output from a given area of cortex depends on temporal coincidence with the patterns of the bottom-up input it receives. If an individual experiences stimuli that do not clearly fit any top-down hypotheses derived from previous experience, a given area of cortex relays the details of the patterns it receives to higher cortical areas; the signals are passed on to the next highest layer and this pattern extends until a match is achieved. As a situation becomes more familiar, the representations of a given level of analysis are shifted to lower cortical areas, freeing higher areas for the detection of high-level patterns. The correct identification of objects, sensations, and processes in the environment is thus based upon probabilistic prediction determined by the accumulation of memories of how the perceptual world is organized and how it operates (Hawkins and Blakeslee, 2004; Purves et al, 2001).

We hypothesize that in schizophrenia, the formation and storage of invariant representations at higher hierarchical levels is insufficient. The higher levels do not provide enough input to lower levels for solving the nature of stimuli, and the lower levels do not provide adequate perceptual details to enable a sufficient establishment of perceptual context (Kraus et al, 2009). Thus, simple information must be sent repeatedly to higher levels for more effortful interpretation. Reduction in the correct identification of percepts in the context of real-world information-processing demands, affords the opportunity for arbitrary internally generated interpretations of reality to intrude upon perception and thought, leading to an accumulation of inaccurate but internally meaningful perceptions that may build upon one another into incorrect beliefs. This failed process may be at the core of the development of hallucinations and delusions. Context-based perceptions of real objects and real events are

reduced in favor of an interpretation of reality that is individually determined and disconnected from the experiences and beliefs shared by others. This, we hypothesize, is the mechanism behind the development of delusions and hallucinations in patients with schizophrenia.

Recent work supports this concept (Javitt, 2009). Patients with schizophrenia have great difficulty in perceiving visual objects among noise and are unable to identify incongruous events in a virtual reality context. Although few studies have addressed whether these cognitive impairments precede the onset of psychosis, there have been some confirming data. Individuals who are soon to develop psychosis experience the perception of more elaborate sequences of verbal stimuli in auditory noise conditions (Hoffman et al, 2007). Cognitive paradigms that measure an individual's ability to distinguish percepts from noise based upon context have particular promise for identifying impairments in learning-dependent predictive perception (Koethe et al, 2009).

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### DISCLOSURE

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Hawkins J, Blakeslee S (2004). *On Intelligence*. Times Books: New York.

Hoffman RE, Woods SW, Hawkins KA, Pittman B, Tohen M, Preda A *et al* (2007). Extracting spurious messages from noise and risk of schizophreniaspectrum disorders in a prodromal population. *Br J Psychiatry* **191**: 355–356.

- Javitt DC (2009). When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. Annu Rev Clin Psychol 5: 249–275.
- Koethe D, Kranaster L, Hoyer C, Gross S, Neatby M, Schultze-Lutter F et al (2009). Binocular depth inversion as a paradigm of reduced visual information processing in prodromal state, antipsychoticnaïve and treated schizophrenia. Eur Arch Psychiatry Clin Neurosci 259: 195–202.
- Kraus M, Keefe R, Krishnan R (2009). Memoryprediction errors and their consequences in schizophrenia. *Neuropsychol Rev* 19: 336–352.
- Purves D, Lotto BR, Williams MS, Nundy S, Yang Z (2001). Why we see things the way we do: evidence for a wholly empirical strategy of vision. *Philos Trans R Soc Lond Biol Sci* **356**: 285–297.

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# New Insights into the Mechanisms Underlying the Effects of BDNF on Eating Behavior

Food intake is a complex behavior resulting from interactions between homeostatic and hedonic regulatory mechanisms acting in the energy balance and reward centers of the brain. Alterations in feeding behavior are often pervasive and can lead to obesity and its associated medical complications, including metabolic and cardiovascular disorders and psychological distress. A compelling body of evidence emerged recently, indicating a pivotal role of brain-derived neurotrophic factor (BDNF) in pathological processes leading to abnormal food intake and excessive weight gain. BDNF signals through the TrkB receptor to promote neuronal survival, differentiation, and synaptic plasticity. Perturbing central BDNF signaling in mice results in hyperphagic behavior and obesity (Xu et al, 2003; Unger et al, 2007). In humans, BDNF haploinsufficiency was linked to elevated food intake and severe weight gain (Han et al, 2008). These findings have significant clinical implications, as the BdnfVal66Met allele, which impedes regulated BDNF secretion, is highly prevalent in humans (Shimizu et al, 2004).